IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

| | | | |
|---|---|---|---|
| Applicant: | Allen, et al. | Examiner: | Wilson, Michael C. |
| Serial No.: | 10/026,937 | Group Art Unit: | 1632 |
| Filed: | December 21, 2001 | Docket: | R632CIP/75658.292 |
| Confirmation No. | 7301 | | |
| Title: | Transgenic Mice Containing FPR-RS4 Gene Disruptions | | |

Mail Stop AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**26619**
PATENT TRADEMARK OFFICE

Sir:

We are transmitting herewith the attached:

☒ Transmittal Sheet
☒ Amendment
☒ Request for Extension of Time for three month(s) and fee
☒ Please charge all fees to Deposit Account No. 502775

| CLAIMS REMAINING AFTER AMENDMENT | | HIGHEST NUMBER PREVIOUSLY PAID FOR | | PRESENT EXTRA | | RATE | | FEE |
|---|---|---|---|---|---|---|---|---|
| **Total Claims** | | | | | | | | |
| 1 | - | 20 | = | 0 | x | 25 | = | $0.00 |
| **Independent Claims** | | | | | | | | |
| 1 | - | 3 | = | 0 | x | 100 | = | $0.00 |
| **Three Month(s) Extension of Time fee** | | | | | | | | $510.00 |
| **Total Filing Fees** | | | | | | | | $510.00 |

Please consider this a PETITION FOR EXTENSION OF TIME for a sufficient number of months to enter these papers or any future reply, if appropriate. Please charge any additional fees or credit overpayment to Deposit Account No. **502775**.

GREENBERG TRAURIG LLP
1200 17th Street, Suite 2400
Denver, CO 80202
303.572.6500

By: _____
Name: John E. Burke
Reg. No.: 35,836

JEBurke/mcn

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

| | | | |
|---|---|---|---|
| Applicant: | Allen, et al. | Examiner: | Wilson, Michael C. |
| Serial No.: | 10/026,937 | Group Art Unit: | 1632 |
| Filed: | December 21, 2001 | Docket: | R632CIP/75658.292 |
| Confirmation No. | 7301 | | |
| Title: | Transgenic Mice Containing FPR-RS4 Gene Disruptions | | |

**AMENDMENT**

MS AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

In response to the Office Action dated February 10, 2006, Applicant respectfully requests entry and consideration of the following amendment and remarks.

**Amendments to the Specification** begin on page 2 of this paper.

**Amendments to the Claims** are reflected in the listing of claims that begins on page 3 of this paper.

**Remarks** begin on page 6 of this paper.

**Amendments to the Specification**

Please replace the paragraph beginning at page 10, line 27, with the following paragraphs:

-- Figures 2A-2B show the sequence of the FPR-RS4 gene (SEQ ID NO:1); the location of the disrupted portion of the FPR-RS4 gene (SEQ ID NO:1, see underlined portion);, as well as the nucleotide sequences flanking the *Neo*$^r$ insert in the targeting construct (see bold portions of SEQ ID NO:1). Figure 2B shows the sequences identified as SEQ ID NO:3 and SEQ ID NO:4, which were used as the 5' and 3' targeting arms (including the homologous sequences) in the FPR-RS4 targeting construct, respectively.--

**Amendments to the Claims:**

This listing of claims will replace all prior versions and listings of claims in the application.

1. (Withdrawn) A targeting construct comprising:

   (a) a first polynucleotide sequence homologous to at least a first portion of an FPR-RS4 gene;

   (b) a second polynucleotide sequence homologous to at least a second portion of the FPR-RS4 gene; and

   (c) a selectable marker.

2. (Withdrawn) A method of producing a targeting construct, the method comprising:

   (a) providing a first polynucleotide sequence homologous to at least a first portion of an FPR-RS4 gene;

   (b) providing a second polynucleotide sequence homologous to at least a second portion of the FPR-RS4 gene;

   (c) providing a selectable marker; and

   (d) inserting the first sequence, second sequence, and selectable marker into a vector to produce the targeting construct.

Claims 3-9 (Canceled)

10. (Withdrawn) A method of identifying an agent that modulates the expression or function of an FPR-RS4 gene, the method comprising:

    (a) providing a non-human transgenic animal comprising a disruption in an FPR-RS4 gene;

    (b) administering an agent to the non-human transgenic animal; and

    (c) determining whether the expression or function of the disrupted FPR-RS4 gene in the non-human transgenic animal is modulated.

11. (Withdrawn) A method of identifying an agent that modulates the expression or function of an FPR-RS4 gene, the method comprising:

    (a) providing a cell comprising a disruption in an FPR-RS4 gene;

    (b) contacting the cell with the agent; and

    (c) determining whether the expression or function of the FPR-RS4 gene is modulated.

12. (Withdrawn) The method of claim 11, wherein the cell is derived from the non-human transgenic animal of claim 6.

13. (Withdrawn) An agent identified by the method of claim 10 or claim 11.

Claims 14-22 (Canceled)

23. (Withdrawn) A method of identifying an agent that ameliorates a phenotype associated with a disruption in an FPR-RS4 gene, the method comprising:

    (a) administering an agent to a transgenic mouse comprising a disruption in an FPR-RS4 gene; and

    (b) determining whether the agent ameliorates at least one of the following phenotypes: increased anxiety, impaired motor coordination or balance, ataxia, or decreased susceptibility to seizure.

24. (Withdrawn) An agent identified by the method of claim 23.

25. (Withdrawn) An agonist or antagonist of FPR-RS4.

26. (Withdrawn) Phenotypic data associated with a transgenic mouse comprising a disruption in an FPR-RS4 gene, wherein the phenotypic data is in an electronic database.

27. (Withdrawn) A method of treating anxiety, the method comprising administering to a subject in need a therapeutically effective amount of FPR-RS4.

28. (Withdrawn) A method of treating impaired motor coordination, impaired balance, or ataxia, the method comprising administering to a subject in need a therapeutically effective amount of FPR-RS4.

29. (Withdrawn) A method of identifying an agent that ameliorates anxiety, the method comprising:

    (a) administering an agent to the transgenic mouse of claim 15; and

    (b) determining whether the agent has an affect on anxiety in the transgenic mouse.

30. (Withdrawn) A method of identifying an agent that ameliorates impaired motor coordination, impaired balance, or ataxia, the method comprising:

    (a) administering an agent to the transgenic mouse of claim 17; and

    (b) determining whether the agent has an affect on motor coordination, balance or ataxia in the transgenic mouse.

31. (Withdrawn) A method of evaluating treatments for anxiety, the method comprising:

    (a) administering a therapeutic agent to the transgenic mouse of claim 15; and

    (b) determining the *in vivo* effects of the agent on anxiety level in the transgenic mouse..

32. (Withdrawn) A method of evaluating treatments for impaired motor coordination, impaired balance, or ataxia, the method comprising:

(a) administering a therapeutic agent to the transgenic mouse of claim 17; and

(b) determining the *in vivo* effects of the agent on motor coordination, balance, or ataxia in the transgenic mouse.

33. (Withdrawn) A method of identifying an agent that inhibits the activity or function of FPR-RS4, the method comprising:

(a) providing a cell expressing FPR-RS4;

(b) contacting the cell with an agent; and

(c) determining whether the agent inhibits the activity or function of FPR-RS4, wherein the agent has an affect on seizure susceptibility.

34. (Amended) A transgenic mouse whose genome comprises ~~comprising~~ a homozygous disruption in ~~an~~ the FPR-RS4 gene, wherein the transgenic mouse exhibits, relative to a wild-type control mouse, at least one phenotype selected from the group consisting of enlarged heart, increased heart weight, increased heart to body weight ratio and myocardial fibrosis~~a heart abnormality~~.

Claims 35-37 (Canceled)

38. (Withdrawn) A method of identifying an agent that ameliorates a heart abnormality, the method comprising:

(a) administering a putative agent to the transgenic mouse of claim 34; and

(b) determining whether the agent has an effect on a heart abnormality in the transgenic mouse.

39. (Withdrawn) A method of treating a heart abnormality, the method comprising administering to a subject in need a therapeutically effective amount of FPR-RS4.

40. (Withdrawn) A pharmaceutical composition comprising an FPR-RS4 protein.

## REMARKS

**Amendments**

Claims 3-9, 14-22 and 35-37 have been canceled; claim 1 has been amended, and claims 1, 2, 10-13, 23-33 and 38-40 have been withdrawn. Upon entry of the amendment, claim 34 will be under consideration. Support for the amended claims can be found in the claims as originally filed.

The foregoing amendments are made solely to expedite prosecution of the application and are not intended to limit the scope of the invention. Further, the amendments to the claims are made without prejudice to the pending or now canceled claims or to any subject matter pursued in a related application. The Applicant reserves the right to prosecute any canceled subject matter at a later time or in a later filed divisional, continuation, or continuation-in-part application.

**Rejections**

***Rejections under 35 U.S.C. § 101***

The Examiner has rejected claims 3-9, 14-22 and 34-37 under 35 U.S.C. § 101 because the claimed invention is allegedly not supported by either a specific or substantial asserted utility or a well-established utility.

Applicant respectfully traverses the rejection. Amended claim 34 is drawn to transgenic mouse whose genome comprises a homozygous disruption in the FPR-RS4 gene, wherein the transgenic mouse exhibits, relative to a wild-type control mouse, at least one phenotype selected from the group consisting of enlarged heart, increased heart weight, increased heart to body weight ratio and myocardial fibrosis.

***1. The Utility Requirement***

The present invention has a well-established utility since a person of ordinary skill in the art "would immediately appreciate why" knockout mice are useful. As a general principle, knockout mice have the inherent and well-established utility of defining the function and role of the disrupted target gene, regardless of whether the inventor has described any specific phenotypes, characterizations or properties of the knockout mouse. This asserted utility is substantial, specific and credible.

Applicant directs the Examiner's attention to a recent NIH press release, wherein the NIH announced it was accessing Deltagen's data derived from its analysis of the mice:

> BETHESDA, Md., Wed., Oct. 5, 2005 - The National Institutes of Health (NIH) today announced contracts that will give researchers unprecedented access to two private collections of knockout mice, providing valuable models for the study of human disease and laying the groundwork for a public, genome-wide library of knockout mice.
>
> Under terms of three-year contracts jointly funded by 19 NIH institutes, centers and offices, Deltagen Inc. of San Alpha-FPR-RS4los, Calif., and Lexicon Genetics Incorporated of The Woodlands, Texas will provide NIH and its scientific partners with access to extensively characterized lines of mice in which a specific gene has been disrupted, or "knocked out." In the first year of the contract, NIH will expend about $10 million to acquire about 250 lines of knockout mice.
>
> For each mouse line, the contractors will provide not only the mouse line itself, but also detailed, objective data on the impact of the specific gene deletion on the mouse's phenotype, which includes appearance, health, fitness, behavior, ability to reproduce, and radiological and microscopic data. Such comprehensive information on such a large group of mice has never been available to public sector researchers, and is expected to greatly accelerate efforts to explore gene functions in health and disease.
>
> "Our decision to procure these knockout mouse lines and data and make them available to the research community will yield tremendous benefits, both in the short and long terms," said NIH Director Elias A. Zerhouni, M.D. "This trans-NIH initiative will place important mouse models into the hands of researchers, speeding advances in the understanding of human disease and the development of new therapies. It also represents a significant step in the direction of launching an international project to systematically knock out all genes in the mouse."
>
> Since the early 1980s, when recombinant DNA technology was used to create the first such animals, knockout mice have proven to be one of the most powerful tools available to study the function of genes and to create mouse models of human disease. Researchers have produced knockout mice with characteristics similar to humans suffering from a wide range of disorders, including cancer, heart disease, neurological disorders and even obesity.

(See Researchers to Gain Wider Access to Knockout Mice Trans-NIH Effort Provides New Models for Understanding Human Disease; http://www.genome.gov/17015131) (copy attached).

Thus, the NIH regards the use of knockout mice obtained from Deltagen in studying gene function to be credible, substantial and specific.

With regard to commercial success, the invention has a substantial "real world use" as demonstrated by: (1) delivery of the claimed invention to at least one large pharmaceutical company (evidentiary support available); and (2) commercial use of DeltaBase by three of the world's largest pharmaceutical companies, Merck, Pfizer and GlaxoSmithKline. DeltaBase incorporates the data set forth in the specification with regard to phenotypic analyses of the claimed mouse.

With respect to commercial use, the Federal Circuit has held:

> A correct finding of infringement of otherwise valid claims mandates as a matter of law a finding of utility under § 101. *See e.g., E.I. du Pont de Nemours & Co. v. Berkley & Co., supra,* 620 F.2d at 1258-61, 205 USPQ at 8-11; *Tapco Products Co. v. Van Mark Products Corp.*, 446 F.2d 420, 428, 170 USPQ 550, 555-56 (6th Cir.), *cert. denied*, 404 U.S. 986, 92 S. Ct. 451, 30 L. Ed. 2d 370 (1971). The rule is not related, as Raytheon argues, to whether a defendant may simultaneously assert non-utility and non-infringement; a defendant may do so. The rule relates to the time of decision not to the time of trial, and is but a ***common sense approach to the law. If a party has made, sold, or used a properly claimed device, and has thus infringed, proof of that device's utility is thereby established.*** *People rarely, if ever, appropriate useless inventions.*
>
> Proof of such utility is further supported when, as here, the inventions set forth in [the] claims . . . have on their merits been met with commercial success.

*Raytheon Co. v. Roper Corp.* 724 F. 2d at 959; see also, *Phillips Petroleum Co. v. United States Steel Corp.*, 673 F. Supp. 1278, 1327, 6 U.S.P.Q.2d 1065 (D. Del. 1987), *affirmed*, 865 F.2d 1247, 9 U.S.P.Q.2d 1461 (Fed. Cir. 1989)); *Brenner v Manson*, 383 U.S. 519, 148 U.S.P.Q. 689, 696 (1966)(a patent system must be related to the world of commerce rather than to the realm of philosophy). See also, *In re Fisher* 76 U.S.P.Q. 2d 1225 (Fed. Cir. 2005)(Fisher did not present any evidence showing that agricultural companies have purchased or even expressed any interest in the claimed ESTs. And, it is entirely unclear from the record whether such business entities ever will.) Unlike *Fisher*, Applicant has submitted evidence that the claimed invention has been purchased and delivered to at least one large pharmaceutical company. Unlike *Fisher*, Appellant has presented evidence that the FPR-RS4 knockout mouse has actually been used in the real world.

As held by the Federal Circuit, common sense dictates that "[i]f a party has made, sold, or used a properly claimed device, and has thus infringed, proof of that device's utility is thereby established. People rarely, if ever, appropriate useless inventions." *Raytheon Co. at* 959. As

people rarely, if ever, appropriate useless inventions, large pharmaceutical companies, rarely if ever, purchase useless inventions.

Thus, the Merck, Pfizer and GlaxoSmithKline regard the use of knockout mice obtained from Deltagen in studying gene function to be credible, substantial and specific.

Applicant respectfully submits that this evidence establishes the utility of the claimed invention.

***2. Specific Utility***

The Examiner argues that the asserted use of studying gene function is not specific.

According to the MPEP, "specific utility" means "specific" to the subject matter claimed as compared to a "general utility" that would be applicable to the broad class of the invention (MPEP 2107.01). Use of the FPR-RS4 +/- and -/- mice to study the function of the FPR-RS4 gene and the association of the FPR-RS4 gene with, for example, heart disease, is specific to this mouse. Even if there were many other genes associated with these phenotypes, only the FPR-RS4 knockout mouse (as opposed to all other knockout mice) would be used to study the specific role of this gene in heart disease. The Examiner is respectfully requested to explain (1) how the asserted utility of determining the function of the FPR-RS4 gene would be applicable to all other knockout mice; and (2) how the asserted use of studying the association of the FPR-RS4 gene with these phenotypes, would be applicable to all other knockout mice. The Examiner is requested to explain **how** all other knockout mice would be used to study the function of the FPR-RS4 gene.

***3. Substantial Utility***

The Examiner argues that studying a gene using a knockout mouse is not a substantial real world use.

As argued above, commercial use of the claimed invention clearly demonstrates a real-world, substantial use.

***4. Summary***

In summary, Applicant submits that the claimed transgenic mouse, regardless of any disclosed phenotypes, has inherent and well-established utility in the study of the function of the

gene, and thus satisfies the utility requirement of section 101. Moreover, Applicant believes that the transgenic mice are useful for studying the function of the target FPR-RS4 gene with respect to the cited phenotypes; and are therefore useful for a specific practical purpose that would be readily understood by and considered credible by one of ordinary skill in the art.

In light of the amendments and arguments set forth above, Applicant does not believe that the Examiner has properly established a *prima facie* showing that establishes that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the Applicant would be specific and substantial. (*In re Brana*; MPEP § 2107).

Withdrawal of the rejections is respectfully requested.

***Rejection under 35 U.S.C. § 112, first paragraph***

Claims 3-9, 14-22 and 34-37 are rejected under 35 U.S.C. § 112, first paragraph. The Examiner alleges one skilled in the art would not know how to use the claimed invention because the claimed invention is not supported by either a specific, substantial or credible asserted utility or a well established utility for the reasons set forth in the utility rejection.

Applicant respectfully traverses the rejection. The claims as amended are directed to a transgenic mouse whose genome comprises a disruption of the FPR-RS4 gene. The claimed invention has a credible specific and substantial utility and it is believed that the claimed invention more than satisfies the utility requirements. Therefore, one skilled in the art would clearly know use to use the invention and could practice the invention without undue experimentation.

Claim 4 and 5 have been canceled, without prejudice, rendering the rejection moot.

The Examiner argues that claims 14-21 and 34-37 do not recite that the disruption causes the phenotype.

The statutory basis of the rejection is not understood as the claims are drawn to a composition of matter which exhibits certain properties. The claims recite a mouse having a disruption in the FPR-RS4 gene wherein the knockout mouse exhibits a phenotype relative to a wild-type control mouse. By implication, the knockout mouse exhibits a phenotype caused by the disruption.

Claims 6, 7, 9 and 14 have been canceled, without prejudice, rendering the rejection moot.

In view of the foregoing, withdrawal of the enablement rejection is respectfully requested.

***Rejection under 35 U.S.C. § 112, first paragraph***

Claims 3-9, 14-22 and 34-37 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly being indefinite.

The Examiner argues that the metes and bounds of the FPR-RS4 gene cannot be determined.

Applicant respectfully disagrees. According to the specification (page 3, para 2.):

> The present invention generally relates to transgenic animals, as well as to compositions and methods relating to the characterization of gene function. Specifically, the present invention relates to genes encoding G-protein coupled receptors (GPCRs). More particularly, the present invention relates to the GPCR N-formylpeptide receptor subfamily and to the GPCR gene referred to herein as FPR-RS4 (SEQ ID NO:1; see Figure 1), which corresponds with the murine FPR-RS4 gene (GI or NID number: 3549283; Accession number: AF071182), as described in *Genomics* 51(2):270-276 (1998), the disclosure of which is incorporated herein by reference. The sequence set forth in Figure 1 has 99% identity (1545/1554 identical) to the murine FPR-RS4 gene sequence deposited in GenBank having GI or NID number 3549283 and Accession number AF071182.

The broader definition cited by the Examiner on page 9 of the specification, is a non-species specific definition intended to describe disruption in any non-human animal (see, e.g., underlined language above). As claimed, the invention is drawn to a mouse having a disruption in the FPR-RS4 gene. According to the Federal Circuit, satisfaction of the written description requirement is measured by the understanding of the ordinary skilled artisan. The description must clearly allow persons of ordinary skill in the art to recognize that the inventor invented what is claimed (*Amgen v. Hoechst Marion Rousel* (65 USPQ2d 1385 (Fed. Cir. 2003)). One skilled in the art would understand that what has been disrupted is the mouse FPR-RS4 gene.

Claims 14 and 21 have been canceled, without prejudice, rendering the rejection moot.

Claim 34 no longer recites "heart abnormality."

Withdrawal of the rejections is respectfully requested.

***Rejection under 35 U.S.C. § 103***

Claims 3-9, 14 and 22 stand rejected as obvious over Gao in view of Gao.

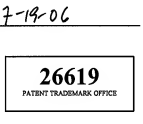
The claims have been canceled, without prejudice, rendering the rejection moot. Withdrawal of the rejection is respectfully requested.

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. **502775**.

Respectfully submitted,

7-19-06
Date




John E. Burke, Reg. No. 35,836
Greenberg Traurig LLP
1200 17th Street, Suite 2400
Denver CO 80202
(303) 685-7411
(720) 904-6111 (fax)